REMARKS

Claims 21-35 are pending. Claims 1-20 were previously canceled. Claims 21, 25, 28, and 32 are amended herein. Claims 23-24, 27, 30-31, 34, and 35 are canceled herein without prejudice. New claims 36 and 37 are presented herein. Accordingly, claims 21, 25, 28, and 32, as amended, and dependent claims therefrom, and new claims 36 and 37 are presently under consideration.

Support for amendment to the claims is found throughout the specification and in the original claims. Specifically, support for amendment to claim 21 is found in previously presented claims 21 and 24 and in paragraph 20. Support for amendment to claim 28 is found in previously presented claims 28 and 31 and in paragraph 20. Claims 25 and 32 are amended to alter dependency cited therein so as to conform to the amendments to the claims presented herein. No issue of new matter is introduced by these amendments.

Support for new claim 36 is found throughout the specification and in the original claims. Specifically, support for claim 36 is found in previously presented claims 21 and 24 and in paragraphs 137-138. Support for new claim 37 is found in previously presented claims 21 and 24 and in paragraph 130 and Figure 1, wherein it is shown that administration of NB-DNJ to Sandhoff mice resulted in an ~21% increase in survival time as compared to that of untreated controls. No issue of new matter is introduced by this amendment.

Priority

The Examiner has indicated that the claim for priority to United States Application No. 10/042,527 and PCT/GB00/01560 under 35 USC § 120, and the claim for priority to United Kingdom Application No. 9909066.4 under 35 USC § 119(a)-(d) are not in compliance with one or more of the conditions for receiving the benefit of an earlier filing date under 35 U.S.C. because these applications do not name a common inventor. In accordance with the Examiner's comments the specification has been amended to delete reference to these applications in the context of the paragraph directed to Related Patent Applications. The inclusion of these applications was the result of a clerical error and did not involve any deceptive intent on the part of Applicant or Applicant's representatives.

The Examiner acknowledges Applicant's claim to foreign priority based on application GB0100889.5 filed in the United Kingdom on 12 January 2001. Enclosed herein

for the Examiner's consideration is a certified copy of priority document GB0100889.5. Applicant believes that the claim to priority for the present application is hereby perfected.

With respect to United Kingdom (U.K.) Application GB0100889.5, Applicant submits herewith a copy of a Petition for Retroactive License, wherein it is indicated that determination of inventorship relating to this U.K. application had not been made at the time of filing and that Steven Walkley, a United States citizen and the inventor of the present invention, was probably an inventor of the U.K. Application GB0100889.5. As indicated by the License for Foreign Filing and Decision on Request, the Petition was granted. Applicant, therefore, asserts that there is compelling evidence that Steven Walkley is an inventor of U.K. Application GB0100889.5.

Rejections under 35 USC § 112

Claims 21-24, 27-31, 34, and 35 have been rejected under 35 USC § 112, first paragraph, for containing subject matter that was allegedly not described by the specification in a manner sufficient to convey that the inventor was in possession of the claimed invention at the time of filing. Claims 23-24, 27, 30-31, 34, and 35 are canceled herein, thereby obviating any rejection of these claims. In view of the amendments to claims, this rejection, as it applied to claims 21-22, and 28-29, is hereby obviated.

The Examiner affirms that the specification provides a detailed description and reduction to practice using imino sugar compounds capable of inhibiting glucosylceramide synthase. In that the claims are amended herein to recite that the inhibitor of glucosylceramide synthesis is an imino sugar, for which the Examiner acknowledges the specification presents detailed written description, Applicant believes that the rejection is nullified and respectfully requests that the rejection be withdrawn.

Claims 21-35 are rejected under 35 USC § 112, first paragraph, for allegedly failing to comply with the enablement requirement. Claims 23-24, 27, 30-31, 34, and 35 are canceled herein, thereby obviating any rejection of these claims. In light of the amendments to the claims and Applicant's arguments presented herein, the rejection under 35 USC § 112, first paragraph, is obviated with respect to claims 21-22, 25-26, 28-29, and 32-33.

The Examiner maintains that the present specification allegedly does not present sufficient support to enable an ordinarily skilled practitioner to practice the invention with respect to claims directed to a method of preventing or curing a mucopolysaccharide disease

in a patient. The instant claims are either maintained as being directed to reducing neuronal glycolipid storage in mucopolysaccharide disease in a patient afflicted with such a disease (claim 28), or amended herein to clarify that the method of the invention relates to reducing pathological features resulting from glycolipid accumulation in a patient with a mucopolysaccharide disease (new claim 36); slowing mucopolysaccharide disease progression in an afflicted patient (claim 21); and to improving survival of a patient with a mucopolysaccharide disease (new claim 37). That being the case, the instant claims are not directed to a method of preventing or curing a mucopolysaccharide disease in a patient. Moreover, Applicant affirms that the instant claims are enabled by the present specification and examples presented therein attest to this assertion.

Accordingly, Example 3 presents evidence demonstrating that the present method reduces neuronal glycolipid storage and reduces pathological features resulting from glycolipid accumulation in a patient with a mucopolysaccharide disease. See paragraphs 131 through to 138. These results are generated in a murine model system of MPS IIIA (Sanfilippo disease). As described in the specification, this murine model system exhibits the disorder's characteristic joint and skeletal storage of proteoglycan fragments, and neuronal storage of GM2 and GM3 gangliosides. Significantly, colonies of mutant mice expressing the MPS IIIA phenotype have been described in many peer reviewed references available in the literature and have been validated by a number of criteria as an authentic model of the disease. Indeed, as stated in the specification, MPS IIIA mice display clinical signs of the disease around 6 months of age with decreased activity, scruffy coat, abdominal distention, hunched posture and waddling gait. By 12 months, the mice exhibit severe ataxia, tremors and weight loss. Death results by 18 months or less.

The Examiner is of the opinion that there is allegedly insufficient evidence to indicate that the instant treatment results in prevention or a cure as reflected in changes in the symptomatic presentation of MPS IIIA mice or that a reduction in GM2 ganglioside in the brain is recognized as a surrogate end point for prevention or cure of MPS IIIA. As indicated herein above, the claims are **not** directed to a method of preventing or curing a mucopolysaccharide disease in a patient. Thus, the Examiner's comments regarding such aspects of the invention are not germane to the instant claims.

Moreover, the Examiner's assertions regarding MPS IIIA mice and what are alleged

to be Applicant's teachings are not consistent with either the specification taken as a whole or the overall opinion of experts in the field of MPS disease. Although the **precise** relationship between the effects of the primary storage material, glycosaminoglycans (GAGS), and other accumulated storage materials on observed disease pathologies is uncertain, it is accepted as a matter of fact that neuronal glycolipid accumulation contributes to disease pathology in Gaucher disease, Sandhoff's disease, Fabry's disease, Tay-Sach's disease, Niemann-Pick C storage disease, and GM1 gangliosidosis. Indeed, these genetic disorders are understood to result from neuronal accumulation/storage of glucosylceramide containing glycolipids. Moreover, mucopolysaccharidoses, which are neurological disorders in which glucosylceramide containing glycolipid accumulation is known to contribute to disease pathology, include Alzheimer's disease, stroke and epilepsy, cancers of neuronal origin such as glioblastoma and astrocytoma, and cancers originating outside neuronal tissue but presenting with neuronal metastases. See paragraph 10. In view of the above, Applicant asserts that the Examiner's interpretation of the teachings of the specification is utterly without basis.

To further underscore Applicant's position regarding the relationship of glucosylceramide containing glycolipid accumulation and disease pathology, Applicant submits for the Examiner's consideration two references from peer reviewed journals: Bhaumik et al. (Glycobiology 9:1389-1396, 1999) and McGlynn et al. (The Journal of Comparative Neurology 480:415-426, 2004). The Bhaumik et al. reference attests to the fact that experts in the field recognize the MPS IIIA mouse as a model system for evaluating pathogenic mechanisms of disease and for testing treatment strategies, including enzyme or cell replacement and gene therapy. See, for example, the abstract on page 1389 and the paragraph bridging pages 1393 and 1394. McGlynn et al. specifically mention that "Murine models of each of these MPS diseases have been discovered (MPS IIIA and MPS VII; Birkenmeier et al., 1989; Bhaumik et al., 1999) or created through gene ablation (MPS I and MPS IIIB; Clarke et al., 1997; Li et al., 1999; Ohmi et al., 2003), **and each bears clinical similarity to the disorders in children**" (emphasis added). See page 416, left column, end of first paragraph. Moreover, the results of McGlynn et al. suggest that the accumulation of gangliosides (e.g., GM2 and GM3) in affected neurons is not simply due to GAG-induced inhibition of select lysosomal enzymes (a secondary effect), but rather is likely to be the

result of defects in the composition, trafficking, and/or recycling of raft components (a primary effect), which indicates possible new mechanisms to explain neuronal dysfunction in MPS disorders. See whole article and Conclusions section bridging pages 424-425, in particular. These findings corroborate and extend previous evidence attesting to the significance of accumulated gangliosides, including GM2, in MPS diseases. In summary, it is well accepted that accumulated gangliosides in affected neurons impair neural function and are a primary causative agent of neurological impairment in individuals afflicted with an MPS disease. It therefore follows that a skilled practitioner would anticipate that a method that reduces ganglioside accumulation in neurons would improve neural function and ameliorate symptoms of an MPS disease.

Further proof as to the enablement of the claimed methods is found in Example 2, which presents results demonstrating that administration of NB-DNJ alone prolongs survival of treated animals in a mouse model for Sandhoff disease. These results also affirm that administration of NB-DNJ slows mucopolysaccharide disease progression in a patient afflicted with such a disease. In brief, untreated animals live a maximum of 140 days, whereas animals treated with NB-DNJ survive a maximum of 170 days. This amounts to a 21% increase in longevity for Sandhoff mice treated with NB-DNJ. See paragraph 130. See also Figure 1, wherein the results of groups of untreated and NB-DNJ-treated Sandhoff mice are graphically depicted. Evidence is, therefore, presented that subjects with an MPS disease that are treated using the method of the present invention display prolonged survival relative to untreated controls. Moreover, Applicant asserts that the reduced lifespan of Sandhoff mice is a consequence of mucopolysaccharide disease progression and, as shown in the instant specification, administration of NB-DNJ slows disease progression as reflected in an increase in longevity.

In view of the above, the instant specification is both enabling of the claimed method and presents experimental evidence demonstrating reduction to practice of the claimed method. As to the Examiner's comments relating to the heterogeneous nature of MPs, it should also be appreciated that these diseases, despite their differences, share common features like the accumulation of glycosaminoglycans (GAGs) and, as shown by McGlynn et al., "secondary and tertiary accumulation of gangliosides (GM2, GM3) and unesterified cholesterol". See Conclusions section at page 424, right column, first sentence. For all of the

above reasons, Applicant asserts that a skilled practitioner would appreciate that the instant claims are enabled by the specification.

In view of the above amendments to the claims and arguments presented herein, Applicant asserts that the rejection of the claims under 35 USC § 112, first paragraph, is untenable and respectfully requests that the rejection be withdrawn.

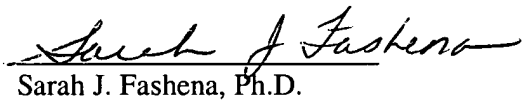
Fees

No additional fees are believed to be necessitated by this amendment. However, should this be an error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment or to credit any overpayment.

Conclusion

It is submitted, therefore, that the claims are in condition for allowance. No new matter has been introduced. Allowance of all claims at an early date is solicited. In the event that there are any questions concerning this amendment, or application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,



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Enclosures: Petition for a One-Month Extension of Time
Certified copy of priority document GB0100889.5
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